REMARKS

Reconsideration of the application is respectfully requested.

The specification has been amended to address an unintentional typographical error that resulted in improper grammar.

Claims 9, 12, 20, and 22 have been canceled without prejudice or disclaimer. Claim 21 has been amended to call for oral administration of the recited bacteria. Support for this amendment is found in the published specification at ¶ 65. New claim 23 has been added. Support for the subject matter called for in new claim 23 is found throughout the published specification, for example, at ¶¶ 7, 86, and 92.

No new matter has been added. Upon entry of this amendment, claims 21 and 23 are pending and at issue.

Rejections under 35 U.S.C. § 102(b)

Claims 9 and 12 have been rejected under 35 U.S.C. § 102(b) as anticipated by JP-92959 (abstract), or alternatively, WO 01/37865.

Without conceding to the validity of this rejection, claims 9 and 12 have been canceled without prejudice or disclaimer thereby rendering this rejection is moot as to these claims.

* * *

Claims 9, 12, and 21 have been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,516,684 ("Saito"). The Examiner contends that Saito discloses a method of treating allergies and lowering antigen-specific IgE by orally administering *L. acidophilus* bacteria of the strain CL92.

Claims 9 and 12 have been canceled thereby rendering this rejection moot as to these claims. As to claim 21, Applicants traverse the rejection and respectfully request reconsideration.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, (Fed. Cir. 1987). Therefore, to expressly anticipate the claimed invention, Saito must disclose each and every limitation of pending claim 21. *See* MPEP § 2131. Additionally, "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily present* in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may result* from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, (Fed. Cir. 1999) (emphasis added).

Applicants respectfully submit that the present claims are not anticipated because Saito fails to disclose the claimed invention, either expressly or inherently.

Saito discloses *Lactobacillus acidophilus* strain CL92, and teaches a method for lowering cholesterol in blood and liver without inhibiting nutrient absorption by orally administering CL92 bacterial cells to a subject. Saito also teaches that CL92 bacterial cells can be used for food, beverages, and animal feed. However, Saito is silent regarding the anti-allergic effect of the CL92 strain. In particular, Saito does not disclose that CL92 bacterial cells are capable of suppressing IgE levels to prevent allergy, and reducing elevated IgE level to treat an already-existing allergy. The present invention calls for a method of reducing allergy by administering CL92 bacteria, which is not disclosed in Saito. Since Saito does not expressly disclose the claimed invention, it does not expressly anticipate the claimed invention.

Also, for the reasons which are discussed in detail below (i.e., different bacterial strains possess different immunological properties), it is improper to conclude that the claimed method for reducing allergy would *necessarily* flow from the methods disclosed in Saito.

Therefore, Applicants respectfully submit that Saito does not anticipate the invention recited in claim 21, either expressly or inherently. Therefore, this rejection should be withdrawn.

Applicants also note that Saito does not disclose the claimed method wherein administration of the lactic acid bacteria reduces elevated antigen-specific IgE levels in blood without significant difference in total IgG. Therefore, Saito also does not anticipate new claim 23.

Rejections under 35 U.S.C. § 103(a)

Claims 9, 12, and 21 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over JP-92959 and/or WO 01/37865 in view of Saito. The Examiner contends that while JP-92959 and/or WO 01/37865 disclose anti-allergy and IgE-lowering methods using certain strains of *L. acidophilus*, the references do not disclose the CL92 specifically. The Examiner relies on Saito as disclosing the CL92 strain of *L. acidophilus*, and concludes that it would have been obvious to modify the methods disclosed in JP-92959 and/or WO 01/37865 to utilize the CL92 strain taught by Saito, thereby arriving at the claimed invention (*see* Office Action, p. 5).

Claims 9 and 12 have been canceled thereby rendering this rejection moot as to these claims. As to claim 21, Applicants traverse the rejection and respectfully request reconsideration.

For a claim to be obvious under U.S. patent law, the Examiner must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. Additionally, the Patent Office must articulate the reason(s) why a skilled artisan "would have recognized" that the results of combining the cited prior art would have yielded "nothing more than predictable results" (*see* Examination Guidelines, Department of Commerce, *Federal* Register, 72(195):57529 (October 10, 2007). Applicants submit that for the following reasons, these requirements have not been satisfied.

1. References Fail to Teach or Suggest that CL92 Bacteria have an Anti-allergic Effect

WO 01/37865 generally teaches anti-allergic effect or suppression of IgE level increase achieved by oral administration of probiotic bacteria, such as *Lactobacillus acidophilus*, through improvement of the intestinal bacterial flora. WO 01/37865 fails to teach a specific strain of *L. acidophilus*, including CL92. JP-92959 generally teaches the effect of lactic acid bacteria, such as *L. acidophilus*, to inhibit the production of IgE antibody.

Neither WO 01/37865 nor JP-92959 disclose an anti-allergy effect of *L. acidophilus*, CL92. Here, it should be noted that the anti-allergic effect of lactic acid bacteria must be determined *for each particular bacterial strain.* That is, even if the anti-allergic effect of one strain of lactic acid bacteria, such as *L. acidophilus*, is disclosed generally, it should not be assumed that each strain of a particular bacterial species demonstrates an equal anti-allergic effect, if any effect occurs at all. In other words, whether bacteria will have an anti-allergic effect is dependent on the particular bacterial strain in question - rather than on the bacterial species.

As support for this position, Applicants submit an article discussing lactic acid bacteria (Inoue, et al., *Abstracts for Annual Meeting of Japan Society for Bioscience*, Biotechnology, and Agrochemistry, 2A20pll:74 (March 2003)), along with an English translation thereof (*see* "**Attachment A**"). Inoue teaches that the effect of lactic acid bacteria on Thl/Th2 balance is dependent on the bacterial strain rather than on the bacterial species. That is, the effect of lactic acid bacteria on suppression of allergic symptoms represented by Thl/Th2 balance is not consistent across all bacterial species, and can only be determined based on the particular bacterial strain. Thus, in absence of disclosure of an anti-allergic effect of the claimed bacterial strain, it is improper to assume that strain CL92 would predictably result in an anti-allergic effect.

Therefore, neither W001/37865 nor JP-92959 would have rendered claim 21 obvious to a skilled artisan, even in view of Saito, because individual bacterial strains have unique anti-allergy properties, and it would have been impossible to predict the effects of the CL92 strain

based on the cited references since none of the references suggests an anti-allergic effect of CL92 bacteria. As stated above, the Patent Office must articulate the reason(s) why a skilled artisan "would have recognized" that the results of combining the cited prior art would have yielded "nothing more than predictable results." Here, a skilled artisan would not have predicted that strain CL92 would result in an anti-allergy effect in view of the prior art cited by the Examiner.

2. Insufficient teaching of JP-92959

Applicants also attach a complete English translation of JP-92959 ("**Attachment B**"). On its surface, JP-92959 appears to teach that any lactic acid bacteria, whether alive or killed, have anti-allergic effects. However, the examples disclosed in JP-92959 teach that the anti-allergic effect of lactic acid bacteria species including *L. acidophilus*, *L. helveticus*, *L. johnsonii*, and *L. rhamnosus*, was demonstrated only *in vitro* using *killed* cells. Based on this disclosure, a person of ordinary skill in the art would not have predicted that administering live *L. acidophilus*, strain CL92, would predictably reduce allergy *in vivo*.

Additionally, Applicants submit herewith an article by Tamura et al., *Int. Arch. Allergy Immunol.*, 143:75-82 (2007) ("**Attachment C**"). In the abstract and page 76, l. col., lines 19-25, it is described that the anti-allergic effect of the *Lactobacillus casei* strain Shirota (LcS) was confirmed *in vitro*, as well as *in vivo* in animal models, but was not confirmed *in vivo* in human subjects. Therefore, based on the prior art cited by the Examiner, a skilled artisan would not have predicted the success of reducing allergy in humans using *L. acidophilus*, strain CL92, based on the *in vitro* experiment as disclosed in JP-95929.

In this regard, WO 01/37865 teaches that the anti-allergic effect of killed cells of *L. acidophilus* was not confirmed *in vivo* (*see* Example 4 and Fig. 4). Viewed in combination with JP-95929, this implies that even if the IgE suppressing effect of *L. acidophilus* was confirmed *in vitro*, it does not mean that any effect observed *in vivo* is sufficiently demonstrated by JP-92959. In the Examples disclosed in the present specification, anti-allergic effect of *L. helveticus*, *L.*

johnsonii, and *L. rhamnosus* was not confirmed *in vivo* even when live bacterial cells were used. This implies that the killed cells of these species do not exhibit the anti-allergic effect *in vivo*. Thus, even if the anti-allergic effect of these species was confirmed *in vitro*, JP-92959 cannot be relied upon as supporting an *in vivo* effect. Therefore, the *in vitro* results disclosed in JP-92959 do not support an *in vivo* anti-allergy effect produced by live bacterial cells.

Applicants therefore submit that JP-92959 would not have led a skilled artisan to predict the success of the claimed invention since JP-92959 cannot be relied upon as demonstrating an IgE-reducing effect *in vivo*. Accordingly, JP-92959 cannot be relied upon as supporting the present obviousness rejection.

3. Exhibition of Effect with Both Live and Killed Cells

WO 01/37865 teaches that improvement of the intestinal bacterial flora by oral administration of live *L. acidophilus* results in an anti-allergic effect or suppression of the IgE levels. The bacteria must be live cells since the effect is achieved through improvement of intestinal bacterial flora. Further, as noted above, the data provided in Fig. 4 demonstrate that live bacteria produce an IgE suppressive effect, whereas killed bacteria do not produce such an effect.

In contrast, the CL92 bacterial strain called for in the present claims produce an anti-allergic using either live or killed cells. The Examples disclosed in the present specification were conducted with live bacterial cells. However, the specification also discloses that the heat-treated product of bacterial cells harvested from a cultured medium, i.e. killed bacterial cells, can be used as the anti-allergic agent of the present invention (*see* specification, page 9, line 26 to page 10, line 3).

To support this disclosure, Applicants submit a declaration by Mr. Fujiwara, wherein the data from an experiment using killed bacteria are presented ("**Attachment D**"). In the experiment, it is demonstrated that CL92 bacteria of the claimed application exhibited anti-allergic effect when bacterial cells killed by heat sterilization were used (*see* Fig. 1). WO

01/37865 does not disclose any specific bacterial strain, still less a bacterial that exhibits an anti-allergic effect using *either* live or killed cells. Since killed bacteria cannot improve intestinal bacterial flora, a bacterial strain that exhibits an anti-allergic effect using killed cells is distinguishable from the effect of bacterial strains disclosed in WO 01/37865.

The mechanism of action that results in the anti-allergic effect of the present invention is different from the mechanism disclosed in WO 01/37865. Thus, it cannot be said that W001/37865 would have suggested to a skilled artisan using CL92 strain which provides an anti-allergic effect using killed cells. Further, the CL92 strain is particularly suitable for products of sterilized type that are distributed at ordinary temperature, and exhibits advantages over bacterial strains that exhibit anti-allergic effect only using live cells, since products containing CL92 bacteria may be stored conveniently and distributed without refrigerating or freezing facilities. Therefore, because a person of ordinary skill in the art would not have recognized that the results of combining WO 01/37865 with the other references were predictable, the present invention is not obvious in view of the prior art cited by the Examiner.

4. Reduction of IgE Level without a Difference in IgG Levels

Examples 2 and 4 of the present application demonstrates that CL92 bacteria are capable of reducing elevated IgE levels without significantly changing IgG levels (*see, e.g.*, Fig. 4). In contrast, WO 01/37865 is silent regarding the administration of any bacterial strains that reduce elevated IgE level without also causing significant changes in IgG levels. Specifically, Example 5 of WO 01/37865 shows that the IgE level is not selectively lowered since the level of IgG decreased in conjunction with suppression of IgE. Stated another way, IgE suppression with concomitant IgG reduction, as disclosed in WO 01/37865, is distinct from selective reduction of elevated IgE level in the present invention. Since the claimed invention calls for the reduction of IgE without causing a significant difference in IgG levels, side effects may advantageously be inhibited.

Further, the IgE reduction disclosed in WO 01/37865 results in the prevention of an allergy *before* it occurs, rather than treating an allergy *after* it develops. In other words, the reduction of elevated IgE results in the treatment of an existing allergy; such a reduction is not disclosed in WO 01/37865. In this regard, Applicants point to the examples disclosed in WO 01/37865, wherein an IgE suppressive effect was measured 24 hours after administering OVA. In contrast, the present application discloses that IgE levels were elevated for as long as 16 days, after which an IgE reducing effect was confirmed. Figs. 1(a) and 1(b) of the present application illustrate that the IgE level is only slightly elevated at 24 hours, in contrast to the disclosure in WO 01/37865.

In view of the foregoing discussion, the examples disclosed in WO 01/37865 merely teaches a method wherein IgE levels are prevented from increasing, rather than being reduced from already elevated levels. To support the advantage of the present invention, i.e., reducing already elevated IgE levels, Applicants submit herewith an article by Kanzato, et al., *Immunobiology*, doi:10.1016/j.imbio.2007.10.001 (2007) (available online Nov. 26, 2007) ("**Attachment E**"). This article teaches that *Lactobacillus acidophilus* L-92 (identical with the CL92 strain) induces apoptosis in Th2 cells, which in turn stimulate B cells to produce IgE through stimulation of dendritic cell. With reference to Kanzato teaching the mechanism of rapid lowering of elevated IgE level using CL92 bacteria, it is understood that the CL92 strain has not only a preventive effect on allergy, but also a treatment effect on allergy due to its ability to lower elevated IgE levels. This aspect of the claimed invention is not disclosed in any of the cited references.

For at least the foregoing reasons, the present invention is not obvious over JP-92959 and/or WO 01/37865 in view of Saito, and Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: February 29, 2008

Respectfully submitted,

By _____

S. Peter Ludwig
Registration No.: 25,351
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant